DIAGNOSIS AND MEDICAL TREATMENT OF BPH

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DISCLOSURE STATEMENT

I have no actual or potential conflict of interest in relation to this program/presentation.
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Benign Prostatic Hyperplasia

- Increased number of epithelial and stromal cells in periurethral area
- May be due to cell proliferation or impaired programmed cell death (molecular etiology uncertain)
- Androgens required for cell proliferation but also actively inhibit cell death
By age 60 >50% of men have BPH

50% of those men have bothersome lower urinary tract symptoms (LUTS)

Can significantly affect quality of life

- Interfere with normal daily activities
- Interfere with sleep patterns

Bothersome symptoms increase with age
Role of Androgens

Development of BPH requires presence of testicular (as opposed to adrenal) androgens

Patients castrated before puberty do not develop BPH

Known fact that androgen withdrawal leads to partial involution of established BPH

In prostate, enzyme 5 alpha reductase converts T into DHT which is necessary for development of BPH
DHT (dihydrotestosterone)

- In prostate tissue, 90% of total prostatic androgen is in form of DHT
- DHT much more potent than T (testosterone)
- Higher affinity for prostatic cellular androgen receptors
- Aging causes a decrease in peripheral T but DHT levels in prostate do not decrease with age
5 alpha reductase
- Prostate nuclear membrane bound enzyme
- Sensitive to inhibition by dutasteride (Avodart) and finasteride (Proscar)
- Converts T to DHT
  - DHT augments effects of various Growth Factors in the prostate
MOLECULAR CONTROL OF PROSTATE GROWTH

Androgens (DHT)

KGF, EGF, IGFs

Cell proliferation
Balanced

Cell death

Estrogens may promote
Normal prostate

Prostate hyperplasia

Androgens (DHT)

KGF, EGF, IGFs

TGF-β

Cell proliferation
Imbalanced

Cell death

Antagonistic

Estrogens may inhibit
Genetic and Familial Factors

- BPH has been shown to have inheritable genetic component (fourfold increased risk of BPH if first degree relative of BPH patient)
- Studies show that inheritable BPH c/w autosomal dominant inheritance pattern
- 50% of <60 yo men who require surgery for BPH have inheritable form of BPH
- Only mammals with BPH – man, dog, lion
### Table 91–3  -- Family History of Early-Onset BPH Increases Risk of Clinical Significant BPH

<table>
<thead>
<tr>
<th>BPH (%)* RELATIVES</th>
<th>Frequency of Clinical BPH</th>
<th>Age-Adjusted</th>
<th>Significance†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Case Relatives</td>
<td>Control Relatives</td>
<td>Odds Ratio (unadjusted)‡</td>
</tr>
<tr>
<td>All first-degree male relatives</td>
<td>28.3</td>
<td>8.6</td>
<td>4.2 (1.7-10.2)</td>
</tr>
<tr>
<td>Fathers of proband</td>
<td>33.3</td>
<td>13.2</td>
<td>3.3 (1.1-10.2)</td>
</tr>
<tr>
<td>Brothers of proband</td>
<td>24.2</td>
<td>3.9</td>
<td>8.0 (1.6-40.5)</td>
</tr>
</tbody>
</table>


* Percent of informative male relatives with history of prostatectomy (open or transurethral) for BPH (60 case relatives and 105 control relatives).
† Chi-square analysis of proportions; Taylor 95% confidence intervals in parentheses.
‡ Cox proportional hazards survival model. Censored outcome—prostatectomy. Time variable—age at death or current age. Values in parentheses indicate 95% confidence intervals.
BPH EVALUATION

Manifestations of Clinical BPH

- LUTS (lower urinary tract symptoms)
- Poor bladder emptying
- Urinary retention
- Overactive bladder
- UTI
- Hematuria
- Renal Insufficiency/Hydronephrosis
- Bladder decompensation (stones, diverticula)
LUTS is a constellation of symptoms which can be caused by BPH or other lower urinary tract pathologic processes.

Differentiation between the two usually possible by History, Physical Exam, U/A.

Additional testing necessary if Dx unclear:
- Uroflow, Bladder scan for PVR, Urodynamic testing, PSA, Cystourethroscopy.
BPH EVALUATION

Medical History should include:
- Voiding history (nocturia, hours in bed, meds(diuretics), FOS, sense of emptying, incontinence, enuresis, UTIs, hematuria)

Physical Exam should include:
- DRE to assess prostate size (1 fb = 10 cc)
- Bladder palpation, percussion
- Peripheral edema
Urinalysis

Check for hematuria, pyuria, bacteria

PSA

For any man with > ten year life expectancy for whom knowledge of presence of PCa would change management

Urine Cytology

In men with irritative symptoms
BPH EVALUATION

- AUA Symptom Index (International Prostate Symptom Score)
  - 8 or greater = moderate to severe symptoms
- Additional tests prior to invasive therapy (usually done by Urologist)
  - Uroflow (< 10 ml/sec is bad)
  - Measurement of PVR by bladder scan
  - Evaluation of upper tracts for hydro if large PVR
  - Cystourethroscopy
  - Serum Creatinine if large PVR (>500 cc)
### International Prostate Symptom Score (I-PSS)

**Patient Name:** __________________________  **Date of birth:** __________  **Date completed:** __________

<table>
<thead>
<tr>
<th>In the past month:</th>
<th>Not at All</th>
<th>Less than 1 in 5 Times</th>
<th>Less than Half the Time</th>
<th>About Half the Time</th>
<th>More than Half the Time</th>
<th>Almost Always</th>
<th>Your score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Incomplete Emptying</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>How often have you had the sensation of not emptying your bladder?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td><strong>2. Frequency</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>How often have you had to urinate less than every two hours?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
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<tr>
<td><strong>3. Intermittency</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>How often have you found you stopped and started again several times when you urinated?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
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<tr>
<td><strong>4. Urgency</strong></td>
<td></td>
<td></td>
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<tr>
<td>How often have you found it difficult to postpone urination?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
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<td><strong>5. Weak Stream</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>How often have you had a weak urinary stream?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td><strong>6. Straining</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>How often have you had to strain to start urination?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
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<tr>
<td><strong>7. Nocturia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>How many times did you typically get up at night to urinate?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>None</th>
<th>1 Time</th>
<th>2 Times</th>
<th>3 Times</th>
<th>4 Times</th>
<th>5 Times</th>
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**Total I-PSS Score**

**Score:**

1-7: *Mild*  
8-19: *Moderate*  
20-35: *Severe*

### Quality of Life Due to Urinary Symptoms

<table>
<thead>
<tr>
<th>Delighted</th>
<th>Pleased</th>
<th>Mostly Satisfied</th>
<th>Mixed</th>
<th>Mostly Dissatisfied</th>
<th>Unhappy</th>
<th>Terrible</th>
</tr>
</thead>
<tbody>
<tr>
<td>If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?</td>
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<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
Initial evaluation
- History
- DRE and focused PE
- Urinalysis
- PSA in select patients

Presence of
- Refractory retention or any of the following clearly related to BPH
- Persistent gross hematuria
- Bladder stones
- Recurrent UTIs
- Renal insufficiency

AUA/IPSS symptom index
Assessment of patient bother

Mild symptoms (AUA/IPSS 7) or no bothersome symptoms

Moderate/severe symptoms (AUA/IPSS 8)

Optional diagnostic tests
- Uroflow
- PVR

Discussion of treatment options

Patient chooses noninvasive therapy
- Watchful waiting
- Medical therapy

Patient chooses invasive therapy
- Minimally invasive therapies
- Optimal diagnostic tests
  - Pressure flow
  - Urethrocystoscopy
  - Prostate ultrasound

Surgery
BPH EVALUATION

Recommendations per decision diagram with following exceptions

- Serum PSA in patients with >10 yr life expectancy for whom dx of PCa would change management
- Urine cytology in men with severe irritative sx
- Serum Creatinine no longer recommended on initial evaluation in standard patient
Management and Treatment Options in BPH

Management of patients with mild to moderate symptoms **without** bother
- If sx do not interfere with daily activity- watchful waiting

Management of patients with bothersome moderate to severe symptoms
- Watchful waiting
- Medical
- Minimally invasive
- Surgical
**BPH Treatment**

- **Medical**
  - Alpha blockers
    - Non selective – dibenzylene, terazosin, doxazosin
      - (Dibenzylene, Hytrin, Cardura)
      - Can cause hypotension, must be titrated, take at hs
      - Excellent for managing patients with BOO and Htx
    - Selective – Tamsulosin, Alfuzosin (Flomax, Uroxatral)
      - Alpha 1e – no need to titrate, start usual dose, first @hs
      - Increases flow rate by 60%
      - Reduces nocturia
      - Decreases PVR
BPH Treatment

Medical

5 alpha reductase inhibitors
- Dutasteride (Avodart) and Finasteride (Proscar)
  - First year decreased sexual function
  - Occasional gynecomastia
  - Decreases PSA to ½ true level over 1 year
  - Reduces prostate volume by 30% over 1 year

Combination

Jalyn (Dutasteride + Tamsulosin)
- Ideal for men with large volume prostate (>40cc) and bothersome LUTS
BPH Treatment

Herbal Remedies

Saw Palmetto

- Leading herbal remedy (annual sales $25 Million)
- Conflicting reports of efficacy in literature
- May increase flow rate in ~ 30% but not as effectively as pharmaceuticals
- Commonly used before seeking medical attention
BPH Treatment

Herbal Remedies

- Zinc, Ginko Biloba, Red Clover, Soy
  - No demonstrated benefit
- Pygeum Africanum (African tree bark)
  - Very popular in Europe, particularly Germany
  - Tree from which it is harvested now endangered
  - Minimal if any objective improvement
    - No increase in flow (Qmax), no reduction in PVR
  - Mechanism of action not understood
BPH Treatment

Minimally Invasive (all thermotherapy based – increase temperature to >45 deg)
- Prostatron (TUMT)
- TUNA (radiofrequency ablation)
- INDIGO (interstitial laser coagulation)

Surgical
- TUIP, TURP
- Open Prostatectomy (suprapubic, retropubic)
- Transurethral electrovaporization
Laser Treatments

- Transurethral laser coagulation (VLAP)
  - High incidence of irritative sx
  - Higher incidence of prolonged catheterization
- Transurethral Laser vaporization
- Transurethral laser resection/enucleation (HOLAP)
Chronic Urinary Retention

Upper tract Hydronephrosis and azotemia

- If bladder overdistended (>700cc) check Creat.
- If creat is increased, admit and watch for post obstructive diuresis
  - Replace 50% of output
  - Check lytes, monitor blood pressure
Special Considerations

- Acute Decompression of overdistended bladder
  - Temporary bladder atony so if > 750cc in bladder, leave catheter indwelling and remove in three to four days after tone returns (start alpha blocker)
  - Check PVRs
  - Expect period of gross hematuria after decompression (usually < 24 hrs)
Bladder Stones

- Usually form secondary to chronic bladder outlet obstruction; require fragmentation
- Benjamin Franklin
  - Invented a catheter for his bladder stone (1752)
  - Made of silver, rubbed with tallow
Frere Jacques

- Lived 1651 – 1714
- French Army (Cavalry)
- Later apprenticed with Italian Lithotomist and became a rapid and facile surgeon
- Adopted clothing and manner of Monks
- Became itinerant lithologist moving from village to village
Four assistants held patient in lithotomy position

Operated on multiple patients/day in front of crowds of 100 – 200 people

In on 4 month period he “cut” 60 patients

25 of 60 died (severed urethras, rectal injuries)

Song reflects need to wake up and move on
Cutting for Stone
PSA SCREENING FOR PROSTATE CANCER
INTRODUCTION

- ACS - 179,300 new cases of prostate cancer diagnosed in 2003 (>40,000 deaths)
- By 2010 – 217,300 new cases /32,000 deaths
- 2013 – 238,600 new cases/29,700 deaths (est CDC)
- Most commonly dx. malignancy in men in the U.S. (1 man in 6 will get the disease)
Currently 1 man in 36 will die of prostate cancer

ACS and AUA recommend an annual PSA and DRE in men >age 50 who have a 10 year or greater life expectancy

Fewer men getting screened because of disagreement among groups that set recommendations (Nat. Ctr for health Statistics)
INTRODUCTION

- PSA and DRE should be offered to younger men at high risk (African American, two or more affected first degree relatives)

- This presentation will show clear benefits of PSA screening and its effect on detection and death rate from prostate cancer
Must demonstrate that screening increases the diagnosis of earlier stage prostate Ca

Must prove that patient survival is prolonged as a result of screening

Must show a decrease in prostate cancer specific mortality rate as a result of screening
Glycoprotein in cytoplasm of prostatic epithelial cells
Prostate (not cancer) specific marker
First released for general use as a laboratory test in 1987
Released by prostatic cells in response to irritation or injury
Causes of PSA Elevation

- BPH (large volume glands)
- Prostate Cancer
- Acute and/or chronic prostatitis
- Infarction
- Recent biopsies
- Ejaculation within 24 hours

**NOT** affected by DRE
PSA is highly sensitive but lacks specificity (false positives resulting in invasive tests)

PSA Density = PSA/ volume of prostate in cc. (Volume occupied by PCa causes a higher PSA than a similar volume of BPH)

PSAD cutoff value = .15

Several studies fail to show improved cancer detection as a result of using PSAD
PSA Derivatives - Age Specific PSA

- Designed to increase sensitivity in younger men and to increase specificity in older men
- Oesterling et al. 1993 correlated PSA with age and prostate volume
- Found that PSA cutoff of 4.0 is too high for younger men and too low for older men.
- This theory supported by multiple studies (Catalona 1994; Partin 1996) - see table #1
# TABLE 1

Age and Race-Specific Reference Ranges for PSA

<table>
<thead>
<tr>
<th>Age</th>
<th>Caucasian (ng/ml)</th>
<th>Japanese (ng/ml)</th>
<th>African American (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 – 49</td>
<td>0 – 2.5 ng/ml</td>
<td>0 – 2.0 ng/ml</td>
<td>0 – 2.0 ng/ml</td>
</tr>
<tr>
<td>50 – 59</td>
<td>0 – 3.5 ng/ml</td>
<td>0 – 3.0 ng/ml</td>
<td>0 – 4.0 ng/ml</td>
</tr>
<tr>
<td>60 – 69</td>
<td>0 – 4.5 ng/ml</td>
<td>0 – 4.0 ng/ml</td>
<td>0 – 4.5 ng/ml</td>
</tr>
<tr>
<td>70 – 79</td>
<td>0 – 6.5 ng/ml</td>
<td>0 – 5.0 ng/ml</td>
<td>0 – 5.5 ng/ml</td>
</tr>
</tbody>
</table>
PSA Derivatives - Race Specific PSA

- Oesterling’s work - only Caucasian men
- Known fact that Asian men have smaller prostates and lower incidence of PCa
- Known fact that African Americans have the highest incidence of PCa in the world
- Oesterling - similar study in Japanese men
- Morgan et al, - similar study in African American men 1996 - see Table #1
PSA Derivatives - PSA Velocity

- Carter et al. noted that patients with BPH have a linear slope of PSA Velocity.
- Patients with PCa have an exponential PSA velocity.
- Must have three or more PSA measurements at least 6 months apart to determine PSAV.
- For PSA of <4.0, PSAV cutoff is 0.75 ng/yr.
- For PSA of >4.0, PSAV cutoff is 0.4 ng/yr.
Free PSA - PSA which is not bound to globulins in serum.

Majority of PSA in serum is bound (approx. 85% Lilja, et al. 1993)

Lilja also noted that the ratio of Free : Total PSA in men with PCa is significantly lower

Therefore, F:T PSA ratios (also called PSA II) improve PSA specificity. Cutoff is 25%
Table 2

% Free PSA and Cancer Probability

<table>
<thead>
<tr>
<th>F:T Ratio (%)</th>
<th>Probability of Cancer (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-10</td>
<td>56</td>
</tr>
<tr>
<td>10-15</td>
<td>28</td>
</tr>
<tr>
<td>15-20</td>
<td>20</td>
</tr>
<tr>
<td>20-25</td>
<td>16</td>
</tr>
<tr>
<td>&gt;25</td>
<td>8</td>
</tr>
</tbody>
</table>

Urology Times Vol. 26, # 4, 1998
Screening - Available Modalities

- DRE - before PSA, the most common test for PCa
- TRUS - transrectal ultrasound
- PSA - screening started in the late 1980’s
Screening by DRE

- Was the most common initial test for PCa before the PSA era
- Major limitation is poor sensitivity for detecting curable disease
- 40-60% of men thought to have localized PCa by DRE actually have local or systemic spread when pathological staging is done
- Disease specific survival in PCa dx by DRE shows no decrease in mortality rate (Gerber)
Initial enthusiasm dampened by the low detection rates for PCa

Further limitation in use of TRUS alone for screening is its invasiveness and expense

Now generally felt to be valuable for its ability to allow accurate anatomic sampling of the prostate when other screening tests are abnormal
Screening by PSA

- Solely responsible for the increase in detection of PCa (Farkas, et al. 1998)
- Dx of pathologically organ confined PCa was 33% in pre PSA era; 70% in post PSA era (Catalona et al. 1993)
- PCa detection rate is 4.6 - 5.0% of all men screened compared to 1.5% by DRE (Catalona et al. 1994)
USPSTF RECOMMENDATIONS

USPSTF = United States Preventive Services Task Force


AUA (American Urologic Association)

“a great disservice to men” (USPSTF Rec)

American Society of Clinical Oncology

Recommends PSA testing if > 10 yr life exp
Number of cases of PCa diagnosed increased dramatically in the post PSA era, peaking in 1992 at nearly 400,000 cases.

Increased proportion of tumors dx by PSA are organ confined at time of dx (70 - 80% compared with 20 - 30 % in pre PSA era)
EFFECTS of PSA SCREENING

- Number of cases of PCa which are already metastatic at time of dx have plummeted (LaBrie et al 1999, Scosyrev et al Cancer 2012; 118: 5768-76)

- Patient survival is prolonged because of lead time bias. (PSA detection provides a 5.5 year lead time in dx of prostate ca- Gann et al. 1995)
EFFECTS of PSA SCREENING

- Reports now conclusively show a decrease in mortality from PCa.
- PCa mortality rates increased until 1992 and have decreased steadily since then (Merrill and Stephenson 2000) (Catalona 2012).
- During that same time many non prostate cancer death rates have increased.
Prostate Ca age-adjusted U.S. mortality rates, 1975-2009

Source: National Cancer Institute Surveillance, Epidemiology, and End Results data (seer.cancer.gov); accessed Dec. 5, 2012
Canadian Data also supports the decrease in mortality from PCa since 1991 and more dramatic since 1996 (Meyer et al. 1999)

Labrie et al. (1999) reported PCa mortality of 49/100,000 man years in unscreened group vs. 15/100,000 man years in PSA screened group over 8 yr follow up (69% difference in favor of PSA screening and early treatment) - Quebec
EFFECTS of PSA SCREENING

Goteburg population based screening trial (The Lancet Oncology 2010 11:725 – 32)

77% 14 year follow up

- 41% decrease in advanced disease in screened group
- 44% decrease in prostate cancer mortality
- Number to treat to save 1 life – 12 (compares favorably with breast cancer screening)
Figure 2: Risk of PCa-specific death in Göteborg screening trial

Source: Reprinted from The Lancet Oncol 2010; 11:730 with permission from Elsevier
USPSTF recommendations against PSA screening are flawed

- They ignore epidemiologic data which show a 44% decrease in prostate cancer mortality (SEER Data July 2012)
- They ignore high risk populations such as strong family history or men of African descent who have a 50% higher incidence and a 200% higher disease spec mortality
CONCLUSION

PSA determination as part of annual health physical has dramatically influenced demographics of PCa and its diagnosis.

All three criteria for successful PCa screening have been met:

- Increase in diagnosis of earlier stage PCa
- Prolongation in patient survival
- Decrease in prostate cancer specific mortality